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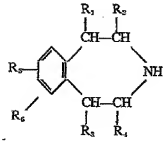
Swiss Patent 500 194

Process for preparing tetrahydroazepine derivatives

The present invention relates to a novel process for preparing tetrahydroazepine derivatives and addition salts thereof with inorganic or organic acids.

No economic preparation process is known to date for 2,3,4,5-tetrahydro-1H-3-benzazepines which have no substituents or, for example, hydrocarbon radicals as carbon substituents in the azepine ring. Though the unsubstituted 2,3,4,5-tetrahydro-1H-3-benzazepine is obtained by high-pressure hydrogenation of 1,2-phenyldiacetonitrile in ammonia with a nickel catalyst [P. Ruggli et al., Helv. Chim. Acta, *18*, 1934 (1935) and *20*, 925-927 (1937)] in good purity, it is obtained in a poor yield. Application of this process to 2,3,4,5-tetrahydro-1H-3-benzazepines which have hydrocarbon radicals as carbon substituents in the azepine ring is unknown and would be uneconomic. The starting materials needed for this purpose would additionally be difficult to obtain. Since, however, such 2,3,4,5-tetrahydro-1H-3-benzazepines have gained considerable significance in the last few years, it has become necessary to develop a simple and economic process for preparing these and similar compounds.

The process according to the invention for preparing 2,3,4,5-tetrahydro-1H-3-benzazepines of the general formula I



(I)

in which

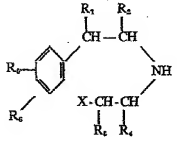
R_1, R_2, R_3 and R_4 are each independently hydrogen, a lower alkyl radical having 1-6 carbon atoms, but preferably an alkyl radical having 1-4 carbon atoms, and at most two of these symbols are a cycloalkyl radical having from 3 to 7 carbon atoms as ring members or a phenyl radical optionally substituted by halogen up to atomic number 35 and/or lower alkyl, or

R_3 and R_4 together are the trimethylene or tetramethylene group,

R_5 is hydrogen, halogen, and

R_6 is hydrogen, halogen up to atomic number 35, a lower alkyl radical or the trifluoromethyl group, where, when R_1, R_2, R_3, R_4 and R_5 are each hydrogen, R_6 cannot be chlorine in the 7 position,

which comprises reacting a phenethylamine derivative of the general formula II



(II)

in which R_1 to R_6 are each as defined above, and X is a halogen atom up to atomic number 35, or an addition salt of such a compound with an inorganic or organic acid, with a Lewis acid at temperatures between 100 and 300°, isolating and if desired converting the end

products of the general formula I thus obtained using an inorganic or organic acid to an acid addition salt.

X as halogen is preferably chlorine or bromine.

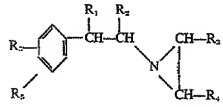
Lewis acids which are useful for the process according to the invention are, for example: antimony(V) chloride, iron(III) chloride, tellurium(II) chloride, tin(IV) chloride, titanium(IV) chloride, tellurium(IV) chloride, bismuth(III) chloride, zinc chloride and especially aluminum chloride, and also corresponding bromides and iodides, and also boron trifluoride or boron trichloride, hydrogen fluoride, sulfuric acid, phosphorus pentoxide or polyphosphoric acid. The Lewis acid is usually added to the reaction mixture in an amount of 0.05-5 mole percent, preferably 1-1.5 mole percent. The reaction temperatures with the Lewis acid are between 100 and 300°, preferably between 150 and 250°.

To isolate the 2,3,4,5-tetrahydro-1H-3-benzazepines formed, the reaction mixture is subsequently admixed with a base, preferably with an inorganic base, for example an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide, or with an alkaline earth metal oxide.

In general, the reaction of a compound of the general formula II with a Lewis acid does not require a solvent or diluent. If desired, however, it is possible to use, as a solvent or diluent, an aliphatic hydrocarbon such as heptane or cyclohexane, nitrohydrocarbons such as nitromethane, nitrocyclohexane or nitrobenzene, or halohydrocarbons such as carbon tetrachloride, ethylene chloride, methylene chloride, o-dichlorobenzene, and also carbon disulfide.

Starting compounds of the general formula II can be prepared, for example, as follows, by, in a manner

known per se, adding a hydrogen halide onto an aziridine derivative of the general formula III



(III)

in which R_1 to R_6 are each as defined under formula I.

The compounds of the general formula III can in turn be obtained analogously to German patent 830 048 (from Herbert Bestian, Ann. 566, p. 238-239) by addition of α,β-alkyleneimines onto styrenes in the presence of alkali metal.

The process according to the invention allows 2,3,4,5-tetrahydro-1H-3-benzazepines to be prepared by a simple and cheap route in a good yield and high purity. A particular advantage is that the starting materials needed for this purpose are readily obtainable. Some of the 2,3,4,5-tetrahydro-1H-3-benzazepines preparable in accordance with the invention are known (P. Ruggli et al. loc. cit.). The known and the novel compounds of the general formula I possess great significance as intermediates for pharmaceuticals.

Compounds of the general formula I are used, for example, as intermediates for the preparation of N-guanidinalkyl derivatives with antihypertensive properties and the unsubstituted 2,3,4,5-tetrahydro-1H-3-benzazepine compound as an intermediate for hypoglycemic arylsulfonylureas (oral antidiabetics).

The as yet unknown 2-methyl-7-chloro-2,3,4,5-tetrahydro-1H-3-benzazepine compound which is covered by the general formula I and salts thereof have anorectic action on oral or parenteral administration.

The 2,3,4,5-tetrahydro-1H-3-benzazepines obtained by the process according to the invention are, if desired, converted in a customary manner to their addition salts with inorganic or organic acids. For example, a solution of 2-methyl-7-chloro-2,3,4,5-tetrahydro-1H-3-benzazepine in an organic solvent is admixed with the acid desired as the salt component or with a solution thereof. Preference is given to selecting, for the reaction, organic solvents in which the salt which forms is sparingly soluble, in order that it can be removed by filtration. Such solvents are, for example, acetone, methyl ethyl ketone, acetone-ethanol, methyl ether or ethyl ether.

For use as medicaments, instead of the free base, it is possible to use a pharmaceutically acceptable acid addition salt, i.e. salts with those acids whose anions are nontoxic at the dosages in question. In addition, it is advantageous when salts for use as medicaments are readily crystallizable and have zero or low hygroscopicity. For salt formation with the 2-methyl-7-chloro-2,3,4,5-tetrahydro-1H-3-benzazepine, it is possible to use, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, β-hydroxyethanesulfonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, mandelic acid and embonic acid.

The novel active ingredients are administered perorally, rectally or parenterally. The daily doses of the free bases or of pharmaceutically acceptable salts thereof vary between 25 and 200 mg for adult patients. Suitable dose unit forms, such as coated tablets, uncoated tablets, suppositories or ampoules, contain preferably 5-50 mg of the inventive active ingredient or of a pharmaceutically acceptable salt.

Dose unit forms for peroral application contain, as the

active ingredient, preferably between 1-90% of 2-methyl-7-chloro-2,3,4,5-tetrahydro-1H-3-benzazepine or a pharmaceutically acceptable salt of this compound. For the production thereof, the active ingredient is combined, for example, with solid pulverulent carriers such as lactose, sucrose, sorbitol, mannitol; starches such as potato starch, corn starch or amylopectin, and also laminaria powder or citrus pulp powder; cellulose derivatives or gelatin, if appropriate with addition of lubricants such as magnesium or calcium stearate or polyethylene glycols, to give uncoated tablets or to give coated tablet cores. The latter are coated, for example, with concentrated sugar solutions which may also comprise, for example, gum arabic, talc and/or titanium dioxide, or with a coating material dissolved in volatile organic solvents or solvent mixtures. Dyes may be added to these coatings, for example to indicate different active ingredient doses.

Suitable further oral dose unit forms include hard gelatin capsules and soft, closed capsules composed of gelatin and a plasticizer such as glycerol. The hard capsules preferably contain the active ingredient as a granule, for example in a mixture with fillers such as corn starch, and/or lubricants such as talc or magnesium stearate, and optionally stabilizers such as sodium metabisulfite ($Na_2S_2O_5$) or ascorbic acid. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as liquid polyethylene glycols, in which case stabilizers can likewise be added.

Useful dose unit forms for rectal application include, for example, suppositories which consist of a combination of the active ingredient or of a suitable salt thereof with a fatty base, or else gelatin rectal capsules which comprise a combination of the active ingredient or of a suitable salt thereof with polyethylene glycols.

Ampoules for parenteral, especially intramuscular, administration preferably comprise a water-soluble salt of the active ingredient in a concentration of preferably 0.5-5%, optionally together with suitable stabilizers and buffer substances, in aqueous solution.

The methods which follow are intended to illustrate the production of uncoated and coated tablets in detail:

a) 250 g of 2-methyl-7-chloro-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride are mixed with 175.80 g of lactose and 169.70 g of potato starch, and the mixture is moistened with an alcoholic solution of 10 g of stearic acid and granulated through a screen. After drying, 160 g of potato starch, 200 g of talc, 2.50 g of magnesium stearate and 32 g of colloidal silica are added and the mixture is pressed to 10 000 tablets each of weight of 100 mg and active ingredient content 25 mg, which, if desired, can be provided with partitioning grooves for finer adjustment of the dosage.

b) 250 g of 2-methyl-7-chloro-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride, 175.90 g of lactose and the alcoholic solution of 10 g of stearic acid are used to produce a granule which, after drying, is mixed with 56.60 g of colloidal silica, 165 g of talc, 20 g of potato starch and 2.50 g of magnesium stearate, and pressed to 10 000 coated tablet cores. These are then coated with a concentrated syrup composed of 502.28 g of crystalline sucrose, 6 g of shellac, 10 g of gum arabic, 0.22 g of dye and 1.5 g of titanium dioxide, and dried. The resulting coated tablets each weigh 120 mg and each contain 25 mg of active ingredient.

The examples which follow describe the inventive preparation of compounds of the general formula I. The temperatures are reported in degrees Celsius.

Example 1

a) 389 g of N-[(2-chloroethyl)phenethylamine] hydrochloride are finely pulverized, mixed with 470 g of aluminum chloride and heated slowly in an oil bath to 180°C (bath temp.) with stirring, and then kept at this temperature for 12 hours. After cooling to approx. 100°, the melt is poured onto ice. The corresponding solution is admixed with 2000 ml of concentrated aqueous sodium hydroxide solution with stirring and, after dissolving the precipitate, extracted with ether. The ethereal solution is dried over magnesium sulfate/potassium carbonate, the desiccant is filtered off and the ether is evaporated. The residue is fractionated under reduced pressure. The resulting 2,3,4,5-tetrahydro-1H-3-benzazepine has b.p. 65°/0.1 torr (m.p. ~ 10°); n_D^{20} = 1.565.
The hydrochloride melts at 248-250°.

The starting substance, N-[(2-chloroethyl)phenethylamine] hydrochloride, is obtained as follows:

b) 900 ml of styrene are added dropwise with stirring to 745 g of ethylenimine and 9 g of metallic sodium; 100 ml thereof are added dropwise rapidly, while the remaining 800 ml are added dropwise at such a rate that the temperature of the reaction mixture is 40-45°C. After the dropwise addition has ended, the mixture is stirred at room temperature overnight. The unconverted sodium is removed mechanically and the excess ethylenimine is distilled off under reduced pressure. The residue is fractionated under reduced pressure. The 1-phenyl-2-(N-aziridinyl)ethane thus obtained has b.p. 48°/0.1 torr; n_D^{20} = 1.5205.

c) 500 ml of methanol are initially charged with stirring and saturated with hydrogen chloride gas in an ice bath. To this are added dropwise, at a temperature of 10-15°, 100 g of 1-phenyl-2-(N-aziridinyl)ethane,

dissolved in 100 ml of methanol. Subsequently, the solution is concentrated to dryness and the residue is dried in an drying cabinet. The resulting N-[(2-chloroethyl)phenethylamine] hydrochloride has, recrystallized from ethanol-glacial acetic acid, m.p. 188-190°.

Example 2

a) 234 g of N-[(2-chloroethyl)-β-methylphenethylamine] hydrochloride are heated to 170° together with 200 g of aluminum chloride for 15 hours. The hot reaction mixture is poured onto ice and alkalized with 2000 ml of 30% aqueous sodium hydroxide solution. A brown oil separates out. The alkaline solution is extracted repeatedly with ether. The combined ether extracts are dried over potassium carbonate/magnesium sulfate, the ether is distilled off and the oily residue is fractionated. The 5-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine thus obtained has b.p. 72°C at 0.6 torr (n_D^{20} = 1.5580).

b) 281 g of 1-phenyl-1-methyl-2-(1'-aziridnyl)ethane (prepared according to example 1b) from α-methylstyrene and ethylenimine) are added to 800 ml of ethyl alcohol saturated with hydrogen chloride gas. The reaction mixture warms up to 30° and a crystalline precipitate forms, the precipitation of which is completed by adding diethyl ether. The precipitate is filtered off and washed repeatedly with ether. The resulting N-[(2-chloroethyl)-β-methylphenethylamine) hydrochloride has m.p. 178-180°.

Example 3

15 g of polyphosphoric acid are heated to 150°and 1 g of N-[(β-chloro-β-phenethyl)phenethylamine hydrochloride is added in portions and, after the addition has ended, the mixture is kept at 150°C for another

half hour. The clear solution is poured onto 15 g of ice, which forms a precipitate. While cooling, the mixture is alkalized with 30% NaOH and the oil which separates out is taken up in methylene chloride. After the methylene chloride has been distilled off, 1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine is distilled at 140-150° under high vacuum.

Example 4

In the manner described in examples 1-4, the corresponding phenethylamine hydrochlorides listed in the 1st column of the table below are obtained analogously from the aziridine derivatives (German patent No. 830 048 and Herbert Bestian, Ann. 566, p. 238-239) are used to obtain the 2,3,4,5-tetrahydro-1H-3-benzazepines listed in the 3rd column:

Phenethylamine hydrochloride	m.p.	2,3,4,5-tertrahydro-1H-3-benzazepine	Physical data
N-[(1'-methyl-2'-chloro-ethyl)phenethylamine] hydrochloride	160-165°	2-methyl-2,3,4,5-tetra-hydro-1H-3-benzazepine	b.p. 60°/0.2 torr
N-[(β-chloro-β-phenethyl)phenethylamine] hydrochloride	168-170°	1-phenyl-2,3,4,5-tetra-hydro-1H-3-benzazepine	b.p. 140-150°/0.01 torr n_D^{20} = 1.4670
N-[(2-chlorocyclohexyl)phenethylamine] hydrochloride	165-167°	2,3,4,4a,5,6,7,11b-octa-hydro-1H-dibenz-[b,d]-azepine	b.p. 150-155°/0.01 torr
N-[(2'-chloroethyl)-α-methylphenethylamine] hydrochloride	149-151°	4-methyl-2,3,4,5-tetra-hydro-1H-3-benzazepine	b.p. 64°/0.2 torr n_D^{20} = 1.5507
N-[(2'-chloroethyl-β-methyl-4-isopropyl-phenethylamine] hydrochloride	184-186°	5-methyl-8-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine	b.p. 71-72°/0.2 torr n_D^{20} = 1.5554

Example 5

a) 30 g of 1-(p-chlorophenyl)-2-(2-chloroethylamino)propane hydrochloride are finely pulverized, mixed with 33.2 g of aluminum chloride and heated slowly in an oil bath to 170-180° (bath temperature) with stirring, and then kept at this temperature for 12 hours. After cooling 100°, the melt is poured onto ice. The resulting solution is admixed with 200 ml of 30% aqueous sodium hydroxide solution with stirring and, after the precipitate has dissolved, extracted with methylene chloride. The methylene chloride solution is dried over magnesium sulfate, filtered and concentrated. The residue is fractionated under reduced pressure. The resulting 2-methyl-7-chloro-2,3,4,5-tetrahydro-1H-3-benzazepine boils at approx. 137°/14 torr; $n_D^{20} = 1.5635$.

The hydrochloride, recrystallized from acetonitrile, melts at 216-218°.

The starting substance, 1-(p-chlorophenyl)-2-(2-chloroethylamino)propane hydrochloride, is obtained as follows:

b) 150 g of aluminum chloride are added to a solution of 56.3 g of chlorobenzene in 200 ml of carbon disulfide. The mixture is brought to boiling at reflux and 79 g of propionic anhydride are added, and then the mixture is boiled at reflux for one hour. The carbon disulfide is distilled off, the residue is poured onto 600 g of ice and 300 g of concentrated hydrochloric acid, and the oil which separates is extracted with benzene. The combined benzene extracts are washed with water, sodium hydroxide solution and again with water, dried over magnesium sulfate, filtered and concentrated by evaporation. The residue is distilled and gives rise to p-chloropropiophenone of boiling point

120°/10 mm Hg.

c) A solution of 57 g of p- chloropropiophenone in 200 ml of methanol is added at approx. 15-20° to a mixture of 8.9 g of sodium borohydride and two potassium hydroxide pellets in 150 ml of methanol over the course of 30 minutes with stirring. The mixture is stirred at 25-30° for 2 hours, stored at room temperature overnight, and then 125 ml of 2N hydrochloric acid are added. The acidic mixture is concentrated by evaporation and the residue is extracted with benzene. The benzene extract is dried over sodium sulfate, filtered and concentrated by evaporation. The residue is distilled and gives rise to 1-(p-chlorophenyl)propanol of boiling point 128-130°/13 mm Hg, n_D^{20} = 1.5368.

d) 54 g of 1-(p-chlorophenyl)propanol are added to 5 g of dry sodium hydrogen sulfate heated to from 220 to 230° under a vacuum of 100-110 mm Hg within 3 hours. The reaction mixture is distilled under a pressure of approx. 14 mm Hg and the distillate is exchanged with diethyl ether. The ether extract is dried over magnesium sulfate and sodium bicarbonate, filtered and concentrated by evaporation. The residue is distilled under reduced pressure and give rise to p-chloro-β-methylstyrene of boiling point 80-82°/15 mm Hg, n_D^{20} = 1.5660.

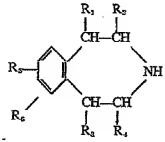
e) 33 g of p-chloro-β-methylstyrene are introduced dropwise at room temperature into a solution of 50 g of dry ethylenimine and approx. 500 mg of metallic sodium with stirring. When the temperature begins to rise after about 2 hours, it is kept at about 30° by external cooling. When the reaction has ended, stirring is continued at approx. 25°C for about another 30 minutes. Unconverted sodium is removed mechanically and excess ethylenimine is removed under reduced pressure. The residue is fractionated under reduced pressure and

gives rise to 1-(p-chlorophenyl)-2-(1-aziridinyl)propane of boiling point 120-121°/14 mm Hg, n_D^{20} = 1.5272.

f) A solution of 39.5 g of 1-(p-chlorophenyl)-2-(1-aziridinyl)propane in 100 ml of ethanol is added at 5°C to 150 ml of a saturated ethanolic hydrogen chloride solution over the course of 15 minutes. The reaction mixture is concentrated by evaporation until crystallization commences, and cooled. The crystals are filtered off and recrystallized from ethanol. The resulting 1-(p-chlorophenyl)-2-(2-chloroethylamino)-propane has a melting point of 189-191°.

MAIN CLAIM

A process for preparing 2,3,4,5-tetrahydro-1H-3-benzazepines of the general formula I



(I)

in which

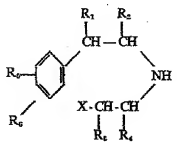
R_1, R_2, R_3 and R_4 are each independently hydrogen, a lower alkyl radical having 1-6 carbon atoms, but preferably an alkyl radical having 1-4 carbon atoms, and at most two of these symbols are a cycloalkyl radical having from 3 to 7 carbon atoms as ring members or a phenyl radical optionally substituted by halogen up to atomic number 35 and/or lower alkyl, or

R_3 and R_4 together are the trimethylene or tetramethylene group,

R_5 is hydrogen, halogen, and

R_6 is hydrogen, halogen up to atomic number 35, a lower alkyl radical or the trifluoromethyl group, where, when R_1, R_2, R_3, R_4 and R_5 are each hydrogen, R_6 cannot be chlorine in the 7 position,

which comprises reacting a phenethylamine derivative of the general formula II



(II)

in which R_1 to R_6 are each as defined above, and X is a halogen atom up to atomic number 35, or an addition salt of such a compound with an inorganic or organic acid, with a Lewis acid at temperatures between 100 and 300°, isolating and if desired converting the end products of the general formula I thus obtained using an inorganic or organic acid to an acid addition salt.

SUBCLAIM

The process according to the main claim for preparing 2,3,4,5-tetrahydro-1H-3-benzazepines of the general formula I, in which R_1, R_2, R_3 and R_4, as lower alkyl radicals, are each independently lower alkyl radicals of 1-4 carbon atoms.

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Note from the Swiss Institute for Intellectual Property:

Should parts of the description be out of line with the definition of the invention given in the main claim, please be reminded that, according to Article 51 of the Swiss Patent Law, the main claim is crucial for the objective validity of the patent.